Prediction of Atherosclerosis Development by Modeling the Metabolism of Lipoproteins

By

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Abstract

Atherosclerosis is the disease related to coronary heart disease and stroke. The initiation of atherosclerosis is induced by physical stimuli which is shear stress on the endothelial cells and by endothelial activation. Development of atherosclerosis and foam cell formation is highly related to lipoprotein metabolism especially the concentration of oxidized low density lipoprotein(oxLDL).

This essay presents an in-depth review of lipoprotein metabolism, including how chylomicron and chylomicron remnant works, how ApoB100 lipoprotein (VLDL, IDL and LDL) works, how high density lipoprotein(HDL) and reverse cholesterol transport works, and how these lipoproteins interact with each other. Moreover, other species and process which play the important role in lipoprotein metabolism such as lipoprotein lipase and beta-oxidation are reviewed.

Then a model of lipoprotein metabolism based on plasma, liver, adipose and muscle compartment is presented. This model was used to analyze how the composition of dietary fat affects oxLDL concentration.

Palm oil, olive oil and corn oil (enriched in saturated, monounsaturated and omega-6 fatty acids) were used as impacts. The result shows that corn oil has the largest amount of both double bond and oxidized double bond after meals which suggests that corn oil and other polyunsaturated fats are related to atherosclerosis.

Thesis Committee

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1.1 Atherosclerosis

1.1.1 Overview

Atherosclerosis, a disease in which plaques accumulate in subendothelial space, or in tunica intima of arteries, is considered as the main factor of peripheral artery disease, coronary artery disease and stroke.[1,2] Atherosclerotic plaque consists of connective tissue, lipids, macrophage cells and immune cells.[3,4] The overall atherosclerosis process can be divided into several key stages.[5]

1.1.2 Initiation

Initiation of atherosclerosis is due to endothelial dysfunction which leads normal endothelial cells lines to become compromised and proinflammatory.[6] There are several factors that promote endothelial dysfunction including endothelial activation, physical stimuli (shear stress) and cytokines. Endothelial activation, by definition, is the increased expression of cell surface adherence proteins such as vascular cell adhesion molecule 1(VCAM-1).[5,7] Endothelial activation is induced primarily by nuclear factor kappa B(NF-κB) which is a group of transcription factors and its activation depend on cytokines.[8] The physical stimulus that promotes endothelial dysfunction is the turbulent flow which commonly occurs at branches and curves of artery whereas lamina flow usually occurs at straight smooth artery wall, and this makes branches and curves in arteries more susceptible to endothelial dysfunction.[9,10]

1.1.3 Development and form cell formation

Endothelial dysfunction will lead to relatively high probability of recruitment, adhesion and migration of monocytes into local subendothelial space due to the increased factors including adhesion proteins and attractant factors.[11-14] Monocytes in the subendothelial space then differentiate into macrophages. In artery intima, Macrophages recognize apoB-containing lipoproteins including low density lipoprotein(LDL), intermediate density lipoprotein(IDL), very low density lipoprotein(VLDL) remnant and chylomicron(CM) by endocytosis through LDL receptors(LDLR) on the surface of macrophages. After uptake, the cholesterol ester(CE) from apoB-containing lipoproteins is hydrolyzed in the lysosomes of macrophages to free cholesterol(FC) which is delivered to the endoplasmic reticulum. In endoplasmic reticulum, FC is esterified to CE.[15,16] The produced CE is stored in the form of droplets. The number and size of droplets inside macrophages is the main indicator of whether these macrophages are converted to foam cells.[17] Formation of foam cells which have excess CE droplets inside is the next step in monocyte recruitment in the overall atherosclerosis process. In normal macrophages, accumulating CE in endoplasmic reticulum triggers reduced endocytosis of ApoB-containing lipoproteins by downregulating the LDLR in order to prevent foam cell formation. But this CE control mechanism only works for LDLR endocytosis process. Modified ApoB-containing lipoproteins especially oxidized LDL(oxLDL) are preferentially bound by specific scavenger receptors such as CD36 which are not affected by the macrophage CE control mechanism.[18,19] The increased amount of modified ApoB-containing lipoproteins, or increased oxLDL, results in excessive accumulation CE droplets inside macrophages and eventually promotes foam cell formation.

1.1.4 Inflammation and thrombus

As the number of foam cells increases, the chemoattractant and growth factors derived from foam cells also increase.[20–23] These chemoattractant and growth factors enhance the infiltration of vascular smooth muscle cells(VSMCs) into the tunica intima from the tunica media. The infiltrated VSMCs then proliferate and form a fibrous cap that covers the foam cells.[24] When the foam cells accumulations area gets large enough, it leads to macrophages death and efferocytosis to produce a necrotic core inside the area.[25,26] In the stable state, the necrotic core is small and the fibrous cap is thick enough to prevent rupture. The appearance of specific inflammatory factors, with increasing age, enlarges the necrotic core by converting the foam cells to their proinflammatory phenotype and increases their susceptibility to apoptosis. Meanwhile, the specific inflammatory factors also weaker the fibrous cap which results in a high possibility of rupture.[27,28] The combination of attenuated fibrous cap and extended necrotic core eventually cause the rupture and thrombus by releasing procoagulation components into the lumen from necrotic core.[29,30]

1.2 Lipoprotein

1.2.1 Overview

Lipoproteins are the primary transporters that deliver cholesterol, triglycerides and other nutrients from blood to tissues. Lipoproteins are classified into Chylomicron, very-low-density lipoprotein(VLDL), intermediate- low-density lipoprotein(IDL), low-density-lipoprotein(LDL) and high-density-lipoprotein(HDL) according to their density. Each lipoprotein has a hydrophobic core which is comprised of cholesterol ester(CE) and triglyceride(TG), and hydrophilic monolayer membrane which is comprised of phospholipid(PL), free cholesterol(FC)

and one or more apolipoproteins. Different types of apolipoproteins including ApoA1, ApoB48, ApoB100, ApoC2, ApoC3 and ApoE penetrate the surface of lipoproteins as transmembrane proteins.

1.2.2 Species in Lipoproteins

Triglycerides are composed of one glycerol and three fatty acids molecules. It is an essential component of body fat storage for energy and plays a key role in beta-oxidation to produce Acetyl-CoA. Cholesterol is a type of sterol. It is used to synthesize hormones as well as to contain cell membrane fluidity. Cholesterol ester is the esterified molecule of cholesterol which consists of one cholesterol molecule combined with one fatty acid molecule. Phospholipid, the main element of cell membrane besides cholesterol, is made by one glycerol molecule, two fatty acid molecules and a phosphate group.

1.2.3 Apolipoproteins in Lipoproteins

ApoA1 is the main protein of pre-HDL and mature HDL. It is produced in the liver and intestine so ApoA1 also is found in chylomicrons. It associates with lecithin cholesterol acyltransferase(LCAT), scavenger receptor1(SR-B1) and ATP-binding cassette protein A1(ABCA1) during the reverse cholesterol transport process. ApoB48 is the main protein in the chylomicrons and chylomicron remnants and is produced in intestine. Each chylomicron or chylomicron remnant only has one ApoB48. ApoB100 is produced in the liver and exists in VLDL, IDL and LDL. It mediates lipoprotein endocytosis via recognition by LDL receptor. There is only one ApoB100 in each VLDL/IDL/LDL. ApoC2 and ApoC3 are the activator and inhibitor of lipoprotein lipase(LPL) that mediate triglyceride hydrolysis process. Both ApoC2

and ApoC3 exist in HDL, VLDL and chylomicron.[31,32] ApoE, exists in IDL, chylomicron remnant and HDL, has the major function promoting lipoprotein endocytosis since it is recognized by LDL receptor.

	CM	VLDL	IDL	LDL	HDL
Volume (L)	8.17E-15	8.70E-17	1.40E-17	8.17E-18	3.20E-19
Mass (g)	7.60E-12	8.70E-14	1.40E-14	8.50E-15	3.52E-19
Concentration (nmol/L)	70	90	100	1200	34000
Molecular Weight (g/mol)	1.50E6	4.00E6	3.50E6	2.75E6	1.75E5
TG (g)	0.4515	0.99	0.316	0.99	1.49
PL (g)	0.03675	0.324	0.261	3.63	9.82
CE (g)	0.021	0.216	0.399	6.93	5.06
FC (g)	0.0105	0.126	0.124	1.32	1.49
Apolipoprotein	ApoB48, ApoA, ApoC, ApoE	ApoB100, ApoC, ApoE	ApoB100, ApoC, ApoE	ApoB100, ApoE	ApoA, ApoC ApoE

Table 1. Physical properties and apolipoproteins in the lipoproteins[33]

1.2.4 Chylomicrons and Chylomicrons Remnants

Chylomicrons play a key role in transporting dietary fat from intestine to diverse organs. Dietary triglycerides are first hydrolyzed to fatty acids by intestinal lipase in the intestinal lumen. Then intestinal cells uptake fatty acids and cholesterol and transfer them to triglyceride and cholesterol ester for further circulation. Triglycerides synthesis requires monoacylglycerol

acyltransferase(MGAT) and diacylglycerol acyltransferase(DGTA) and cholesterol ester synthesis requires ABCA1 in the intestinal cells.[34] Triglycerides, cholesterol esters, ApoB48, ApoA1 and other components are assembled in the endoplasmic reticulum with the help of microsomal triglyceride transfer protein(MTP).[35] Then chylomicrons are secreted to lymph and finally transported to plasma through thoracic duct.[36,37] In the plasma, chylomicrons acquire ApoC and ApoE from HDL by cholesterol ester transfer protein(CETP). In this CETP mediates exchange process, CETP also transfers cholesterol ester from HDL to chylomicron and transfers ApoA1 as well as triglyceride to HDL. The 'mature' chylomicrons that have all the apoproteins needed are then transported to different organs.[38] In muscle and adipose tissue, LPL is synthesized and attached on the capillary vessel wall. LPL hydrolyze triglyceride from chylomicron to free fatty acids with the help of ApoC2. Muscle cells and adipocytes uptake the produced free fatty acids by fatty acid transport protein(FATP) for further metabolism or storage. Once the triglyceride concentration inside chylomicron reaches around one fifth of its original amount, ApoC3 carried by chylomicrons will cease the hydrolysis and all the ApoC will dissociate. These chylomicrons with reduced triglycerides and only ApoB48 and ApoE are called chylomicron remnants.[39] LDL receptors on the surface of hepatocytes recognize and bind ApoE on the chylomicron remnants to promote the endocytosis.[40-44]

1.2.5 ApoB100-containing Lipoproteins

VLDL, IDL and LDL are the ApoB100-containing lipoproteins that deliver triglycerides and cholesterol from liver to other organs. Nascent VLDL is assembled in the hepatocyte endoplasmic reticulum utilizing the ApoB100, triglycerides, cholesterol esters, phospholipids and free cholesterol in the liver. The VLDL synthesis also requires MTP.[45,46] After VLDL is

secreted into blood stream, it acquires ApoC and ApoE from HDL by CETP transferring. CETP also transfers cholesterol esters from HDL to VLDL and triglycerides from VLDL to HDL.[47] Like chylomicrons, triglycerides in VLDL undergo hydrolysis when VLDL binds to lipoprotein lipase with the help of ApoC2 in muscle and adipose capillaries. The free fatty acids produced then will be taken up by muscle cells and adipocytes for further utilization. The original mature VLDL particles are triglyceride-rich micelles with triglycerides being about 55% of the composition.[48] Once triglycerides in the VLDL are removed and drop to one third of original amount by lipoprotein lipase hydrolysis, the VLDL then becomes IDL and ApoC on the it will dissociate.[49] IDL in the blood stream is either endocytosed by the liver when ApoE on IDL binds to LDL receptors on hepatocytes, or further hydrolyzed by hepatic lipase(HL) in the plasma. The further hydrolyzed IDL has more triglycerides removed and becomes LDL which is a cholesterol ester-rich lipoprotein.[50] About 50% of the LDL compositions are cholesterol esters. When IDL becomes LDL, ApoE on its surface dissociates. Although LDL doesn't have ApoE on its surface, it could be endocytosed and cleared by LDL receptors since LDL receptors also recognize and bind ApoB100. However, the binding affinity between ApoB100 and LDL receptors is much lower than that between ApoE and LDL receptors. This results in a long retention time in the plasma for LDL since LDL receptors always preferentially bind IDL and chylomicron remnants or even VLDL and chylomicrons which have ApoE on their surfaces.[51,52] Eventually, the long retention time of LDL makes LDL more susceptible to be taken up by macrophages or be modified to oxidized LDL(oxLDL) and induce further atherosclerosis.

1.2.6 High density lipoprotein

HDL plays an important role in the reverse cholesterol transport and cholesterol balance since HDL is the main carrier of cholesterol from peripheral tissues to the liver. HDL metabolism begins with the synthesis of ApoA1 with LCAT which mainly occurs in the liver. ApoA1 is the main structural and functional protein of HDL.[53,54] Newly produced ApoA1 acquires cholesterol and phospholipid from peripheral tissues to form the nascent HDL with basic structure. This cholesterol and phospholipid efflux process requires ABCA1.[55] ABCA1 genes are expressed in diverse organs. The early extracted cholesterol from tissues to nascent HDL are free cholesterol that located on the surface of HDL. To become mature HDL with larger size and cholesterol ester core, LCAT inside HDL transfers a fatty acid from phospholipids to free cholesterol which results in cholesterol ester production in the core.[56] Apo A1 is the activator of LCAT.[57] The nascent HDL with enough cholesterol ester inside then becomes mature HDL. Besides the cholesterol extraction in the nascent stage with the assistance of ABCA1, mature HDL also can extract cholesterol and phospholipid from tissues by ATP-binding cassette transporter G1(ABCG1) and SR-B1, or even passive diffusion through the cell membrane.[58] In addition to cholesterol and phospholipid extraction, mature HDL has components exchange with chylomicron and VLDL via CETP. Cholesterol esters are transferred from HDL to ApoB containing lipoprotein and triglycerides are transferred from ApoB containing lipoprotein to HDL. The triglycerides in the HDL can be hydrolyzed by hepatic lipase. There are basically two ways for mature HDL to deliver cholesterol to liver. First, HDL binds to SR-B1 on the surface of hepatocytes. SR-B1 mediates the uptake process of cholesterol from HDL to the liver. SR-B1 is a bidirectional receptor since it mediates both efflux and influx of cholesterol between HDL and tissues.[59] The cholesterol empty HDL then will back into

circulation again. Another way for mature HDL to deliver cholesterol to liver is endocytosis because HDL has ApoE which can be recognized by LDL receptors on hepatocytes. All the components of HDL then will be utilized by liver. HDL is regarded as the beneficial micelle in the lipoproteins family contrary to LDL due to the reverse cholesterol transport function of HDL. However, besides reverse cholesterol transport, HDL also has the functions on anti-oxidation of LDL, vasodilatory promotion, anti-thrombosis, cell apoptosis reduction and anti-inflammation.[60]

1.3 Lipoprotein lipase and hepatic lipase

Lipoprotein lipase is the enzyme mainly produced by adipose tissue and muscle. It is the enzyme for triglycerides hydrolysis of VLDL and chylomicron.[61] In adipose tissue or muscle cells, inactive lipoprotein lipase is first assembled in the endoplasmic reticulum. Since lipoprotein lipase is a homodimer, the assembly process includes dimerization and glycosylation.[62,63] Then the inactive assembled lipoprotein lipase is delivered to Golgi apparatus for activation. After activation, lipoprotein is secreted and transported to the surface of vascular endothelial cells. On the vascular wall, lipoprotein lipase attaches the surface by binding to heparin sulfate proteoglycan(HSPG), which is multifunctional glycoprotein containing covalently attached heparan sulfate chains.[64,65] HSPG, located on the cell surfaces, has the functions including constituting cell membrane, maintaining proteases, and binding cytokines or growth factors.[66] To hydrolyze triglycerides inside lipoprotein, lipoprotein lipase also requires ApoC2 as a co-factor. Lipoprotein lipase is regulated by diverse factors. It is regulated during transcription and translation processes. Life stage, fasting as well as insulin level also play an important role in lipoprotein lipase activity regulation. For example, there is liver expression of lipoprotein lipase during fetal stage of humans while there is no liver expression for adults.

During fasting, the lipoprotein lipase activity is low in adipose tissue while it is high in muscle and heart tissue. When eating, in contrast, the lipoprotein lipase activity is high in adipose tissue but it is relatively low in heart and muscle tissue.[67] Insulin as well as glucose has the effect on increasing lipoprotein lipase activity in adipose tissue.[68,69] Hepatic lipase is another member of lipolytic enzyme family which is mainly produced in the liver. Hepatic lipase is the main triglycerides-hydrolysis enzyme for IDL and HDL. Similar to lipoprotein lipase, hepatic lipase is assembled in the endoplasmic reticulum and Golgi apparatus and attached to HSPG on the surface of liver endothelial cells.[70] But the surface of endothelial cell is not the only effective site of hepatic lipase, it could be dissociated by HDL and be active in the circulation system. The activity of circulating hepatic lipase is associated with both HDL and fasting.[71,72] In the feeding state, most ApoE on HDL are transferred to VLDL by CETP, and the ApoE-deficient HDL has a high affinity to associate with hepatic lipase and release hepatic lipase from surface of liver endothelial cells. After releasing, the hepatic lipase associated with HDL is inactive, and its activation and dissociation from HDL depends on plasma electrostatic situation. When eating, intake of free fatty acids increases the negative charge in plasma which then promotes the activation and dissociation of HDL-bound hepatic lipase. While in fasting, ApoE-rich HDL has a low affinity to hepatic lipase and cannot release it from the surface of liver endothelial cells.[73-75]

1.4 Fatty acids and beta oxidation

In people's daily diet, fatty acids are mainly from intake of animal fats and vegetable oils. Fatty acids from diverse resources are divided into several types based on chemical structure. Fatty acids can be broadly divided into saturated fatty acids and unsaturated fatty acids based on whether there is double bonds in long carbon chains. Saturated fatty acids, by definition, don't

have any double bonds in long carbon chain. The most common saturated fatty acids are palmitic acid, lauric acid and stearic acid. Unsaturated fatty acids, contrary to saturated fatty acids, have one or more double bonds in carbon long chain, and it could be first classified by configuration. The unsaturated fatty acids that have trans geometric configuration are commonly referred as trans fats which were widely used in late twentieth century but have been recognized as harmful and coronary artery disease induced species in recent years. The unsaturated fatty acids that have cis geometric configuration could be further divided based on the numbers of double bonds in long carbon chain they have. Monounsaturated fatty acids have only one double bonds in their long carbon chain. There are two common types of monounsaturated fatty acids: omega-7 fatty acids and omega-9 fatty acids. Omega-7 fatty acids have the double bonds between seventh and eighth carbon in the long chain while omega-9 fatty acids have the double bonds between ninth and tenth carbon in the long chain. Common omega-7 fatty acids are palmitoleic acid and vaccenic acid and common omega-9 fatty acids are oleic acid and erucic acid. Polyunsaturated fatty acids have more than one double bonds in the long carbon chain and they are classified into omega-3 fatty acids and omegra-6 fatty acids based on the position of first double bonds. Omega-3 fatty acids have the first double bonds between third and fourth carbon in the long chain and common omega-3 fatty acids are alpha-linolenic acids which are from plant and docosahexaenoic acids(DHA) which are from fish.[76] Omega-6 fatty acids have the first double bonds between sixth and seventh carbon in long chain and common omega-6 fatty acid is linoleic acid. In adipose and muscle tissue, fatty acids are mainly from hydrolysis of triglycerides delivered by lipoproteins, and fatty acids in these tissues whether stored as triglycerides by combining three fatty acids with one glycerol or go through beta-oxidation process.[77] In beta-oxidation, fatty acids with long chains are separated into several two-carbon units. Each two-

carbon unit reacts with co-enzyme A and produce an Acetyl-CoA which reacts as the initial reactants in citric acid cycle to produce ATP.[78,79]

1.5 Oxidation of fatty acids and phospholipids in lipoprotein

In recent research, oxidized LDL takes place of LDL and becomes a more effective biomarker to predict cardiovascular disease since oxidized LDL has a more direct relationship with macrophages and species in intima where atherosclerosis develops. Measurements and experiments also show significant elevations of oxidized LDL in patients with coronary artery disease.[80,81] The surface of lipoprotein mainly consists of phospholipid that has polyunsaturated fatty acid tails. Since the polyunsaturated fatty acids have the high susceptibility to oxidation by reactive oxygen species or free radicals, the polyunsaturated fatty acid easily become fatty acid radical by attaching free radical. Then fatty acid radical will react with molecular oxygen and produce peroxyl fatty acid radical. Finally, peroxyl fatty acid radical reacts with other unsaturated fatty acid to produce oxidized phospholipids or reactive lipid aldehydes such as malondialdehyde(MDA) which are able to modify apolipoproteins such as ApoB100.[82,83] LDL with modified apolipoproteins cannot be recognized by LDL receptors and cleared by the lipoprotein circulating system so eventually these LDL with modified apolipoproteins will only be taken up by macrophage through scavenger receptors in intima and promote the development of atherosclerosis. LDL also can be oxidized by specific oxidase such as myeloperoxidase(MPO).[84] The oxidation process occurs almost always in the subendothelial space or intima where most antioxidant species don't exist.[85] Molecular antioxidants such as vitamin E and enzyme antioxidant such as paraoxonases(PON) all exist and circulate in the plasma so it is almost impossible for LDL to be oxidized in plasma.[86]

Chapter 2. Modeling

2.1 Overview

Based on the lipid metabolism in the human body, we built a model for the circulation of lipoproteins. This model includes liver, muscle, adipose and plasma. The liver compartment takes chylomicron remnant which contains mainly triglycerides and abstracts cholesterols from HDL that is returned from tissue. Liver is also the compartment that produces VLDL which delivers triglycerides from liver to tissues. Muscle and adipose tissue are the main compartments that take up triglycerides in VLDL/IDL/LDL and hydrolyze triglycerides into fatty acids for further energy synthesis or for storage. Plasma is the media transports all types of lipoprotein.

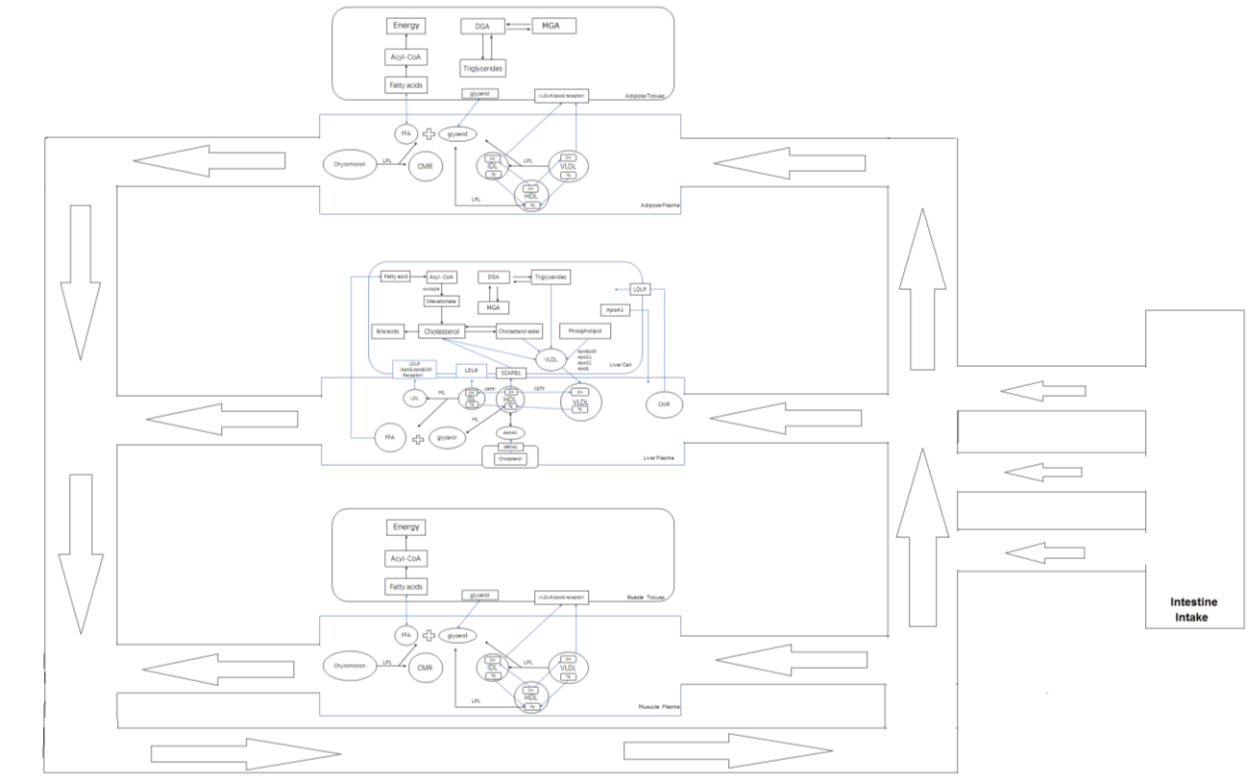


Figure 1. Overall diagram of compartments in the human body

The model includes all cholesterol-related metabolism processes and substances into a schematic for each tissue compartment. Based on the figure of each compartment, biology processes are

derived and then translated into reaction rate equations. Eventually, reaction rate equations from each compartment are combined and related together to develop an ODE model which is capable to model and approximate the concentrations of lipoproteins in the entire body.

2.2 Liver

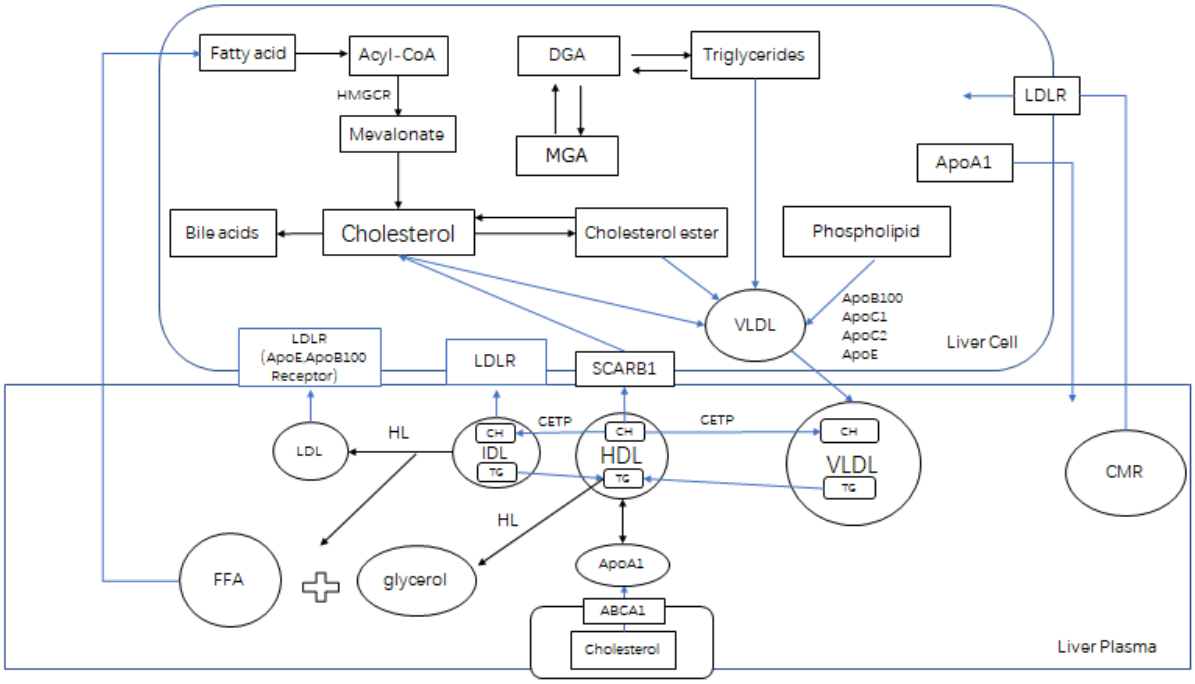


Figure 2. Diagram of liver compartment

Liver

1. **Unsaturated triglyceride oxidation**

Unsaturated triglyceride + [o] ⟶ oxidized triglyceride

2. **Unsaturated cholesterol ester oxidation**

Unsaturated cholesterol ester + [o] ⟶ oxidized cholesterol ester

3. **Saturated triglyceride hydrolysis**

Saturated triglyceride ⟶ 3 Saturated Fatty acids + Glycerol

4. **Unsaturated triglyceride hydrolysis**

Unsaturated triglyceride ⟶ 3 Unsaturated Fatty acids + Glycerol

5. **Saturated cholesterol ester production**

Cholesterol + Saturated Fatty acid ⟶ Saturated cholesterol ester

6. **Unsaturated cholesterol ester production**

Cholesterol + Unsaturated Fatty acid ⟶ Unsaturated cholesterol ester

7. **MGA/DGA/TG balance**

Fatty acid + Glycerol ⟷ Monoglyceride
Fatty acid + Monoglyceride ⟷ Diglyceride
Fatty acid + Diglyceride ⟷ Triglyceride

8. **VLDL assembly**

Triglyceride + Cholesterol ester + phospholipid + ApoB100 ⟶ VLDL

9. **Beta-oxidation**

Saturated Fatty acid ⟶ nAcetyl-CoA
Unsaturated Fatty acid ⟶ nAcetyl-CoA

10. **Citric acid cycle**

Acetyl-CoA ⟶ ATP

11. **Mevalonate pathway**

3Acetyl-CoA ⟶ Mevalonic acid

12. **CETP transfer process**

2Saturated triglyceride + Cholesterol ester loading CETP ⟶ Saturated triglyceride loading CETP + 2Cholesterol ester
2Unsaturated triglyceride + Cholesterol ester loading CETP ⟶ Unsaturated triglyceride loading CETP + 2Cholesterol ester
2Cholesterol ester + Saturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Saturated triglyceride
2Cholesterol ester + Unsaturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Unsaturated triglyceride

As figure 2 shows, the liver compartment is mainly divided into two sections, hepatocytes and hepatic capillary. In hepatic capillary, the processes included are VLDL metabolism, HDL metabolism and CETP exchange process. In VLDL metabolism, VLDL becomes IDL by giving

up triglycerides which are hydrolyzed by lipoprotein lipase, and IDL either becomes LDL by giving up triglycerides which are hydrolyzed by hepatic lipase, or IDL is directly endocytosed by LDL receptors. HDL is assembled by ApoA1 and cholesterols as well as phospholipids which are extracted from tissues, and eventually HDL is taken up by SR-B1. CETP transfers cholesterol esters from HDL to both VLDL/IDL and transfers triglycerides back to HDL from VLDL/IDL. In hepatocytes, the processes included are VLDL assembly, beta-oxidation and balance reaction among monoglycerides(MGA), diglycerides(DGA) and triglycerides. In VLDL assembly, triglycerides, phospholipids, cholesterol esters, cholesterols and specific apolipoproteins that exist in hepatocytes are utilized to synthesize VLDL. In beta-oxidation, fatty acids are utilized to produce Acetyl-CoA. Besides, there are also CMR/VLDL/IDL/LDL/HDL endocytosis and ApoA1 synthesis inside hepatocyte.

2.3 Adipose tissue

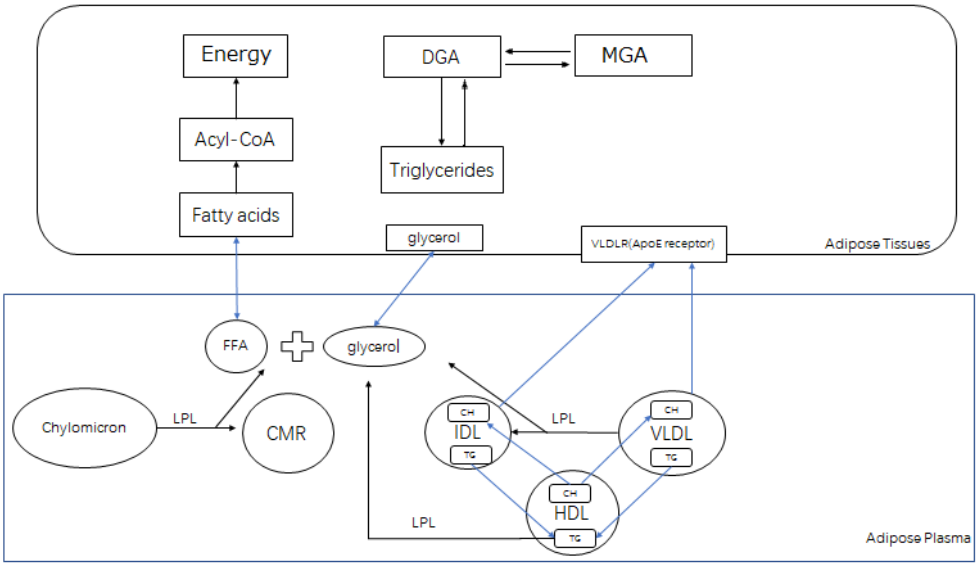


Figure 3. Diagram of adipose tissue

Adipose Tissue

1. **Unsaturated triglyceride oxidation**

Unsaturated triglyceride + [o] ⟶ oxidized triglyceride

2. **Unsaturated cholesterol ester oxidation**

Unsaturated cholesterol ester + [o] ⟶ oxidized cholesterol ester

3. **Saturated triglyceride hydrolysis**

(LPL)

Saturated triglyceride ⟶ 3 Saturated Fatty acids + Glycerol

4. **Unsaturated triglyceride hydrolysis**

Unsaturated triglyceride ⟶ 3 Unsaturated Fatty acids + Glycerol

5. **Saturated cholesterol ester production**

Cholesterol + Saturated Fatty acid ⟶ Saturated cholesterol ester

6. **Unsaturated cholesterol ester production**

Cholesterol + Unsaturated Fatty acid ⟶ Unsaturated cholesterol ester

7. **MGA/DGA/TG balance**

Fatty acid + Glycerol ⟷ Monoglyceride
Fatty acid + Monoglyceride ⟷ Diglyceride
Fatty acid + Diglyceride ⟷ Triglyceride

8. **Beta-oxidation**

Saturated Fatty acid ⟶ nAcetyl-CoA
Unsaturated Fatty acid ⟶ nAcetyl-CoA

9. **Citric acid cycle**

Acetyl-CoA ⟶ ATP

10. **CETP transfer process**

2Saturated triglyceride + Cholesterol ester loading CETP ⟶ Saturated triglyceride loading CETP + 2Cholesterol ester
2Unsaturated triglyceride + Cholesterol ester loading CETP ⟶ Unsaturated triglyceride loading CETP + 2Cholesterol ester
2Cholesterol ester + Saturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Saturated triglyceride
2Cholesterol ester + Unsaturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Unsaturated triglyceride

As figure 3 shows, the adipose compartment also is divided into two sections, adipose tissue and adipose capillary. In adipose capillary, the processes included are VLDL metabolism, chylomicron metabolism and CETP exchange process. In VLDL metabolism, VLDL becomes IDL by giving up triglycerides which are hydrolyzed by lipoprotein lipase, and IDL either

becomes LDL by giving up triglycerides which are hydrolyzed by hepatic lipase, or IDL is directly endocytosed by receptors. Chylomicron becomes chylomicron remnant by giving up triglycerides which are hydrolyzed by lipoprotein lipase. CETP transfers cholesterol esters from HDL to both VLDL/IDL and transfers triglycerides back to HDL from VLDL/IDL. In adipose tissue, the processes included are beta-oxidation and balance reaction among monoglycerides(MGA), diglycerides(DGA) and triglycerides. In beta-oxidation, fatty acids are utilized to produce Acetyl-CoA.

2.4 Muscle

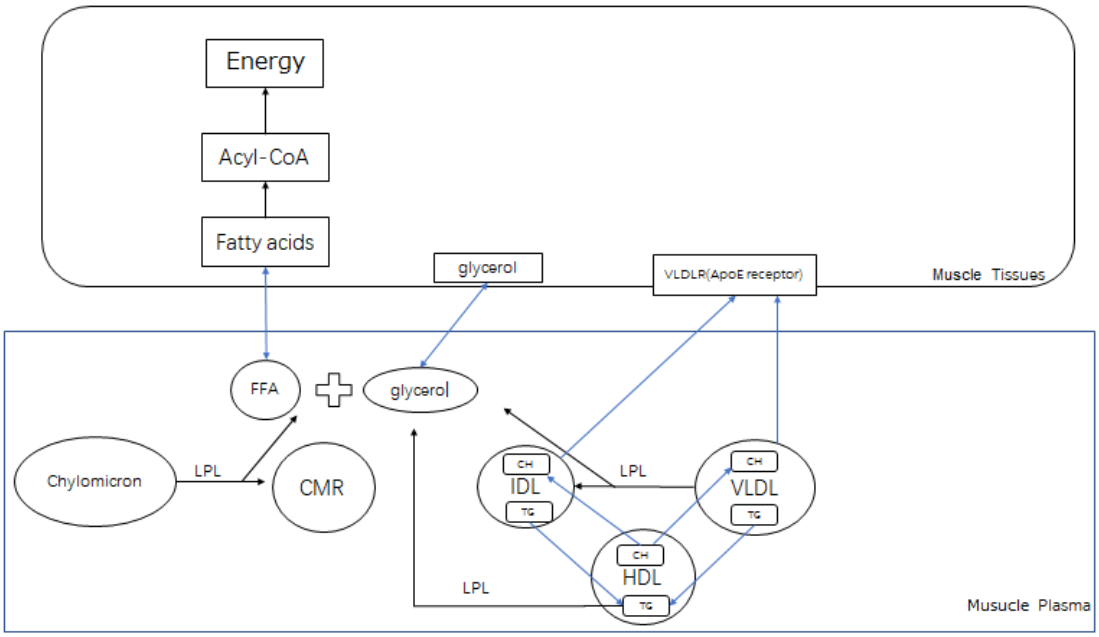


Figure 4. Diagram of muscle tissue

Muscle

1. **Unsaturated triglyceride oxidation**

Unsaturated triglyceride + [o] ⟶ oxidized triglyceride

2. **Unsaturated cholesterol ester oxidation**

Unsaturated cholesterol ester + [o] ⟶ oxidized cholesterol ester

3. **Saturated triglyceride hydrolysis**

Saturated triglyceride ⟶ 3 Saturated Fatty acids + Glycerol

4. **Unsaturated triglyceride hydrolysis**

Unsaturated triglyceride ⟶ 3 Unsaturated Fatty acids + Glycerol

5. **Saturated cholesterol ester production**

Cholesterol + Saturated Fatty acid ⟶ Saturated cholesterol ester

6. **Unsaturated cholesterol ester production**

Cholesterol + Unsaturated Fatty acid ⟶ Unsaturated cholesterol ester

7. **Beta-oxidation**

Saturated Fatty acid ⟶ nAcetyl-CoA

Unsaturated Fatty acid ⟶ nAcetyl-CoA

8. **Citric acid cycle**

Acetyl-CoA ⟶ ATP

9. **CETP transfer process**

2Saturated triglyceride + Cholesterol ester loading CETP ⟶ Saturated triglyceride loading CETP + 2Cholesterol ester

2Unsaturated triglyceride + Cholesterol ester loading CETP ⟶ Unsaturated triglyceride loading CETP + 2Cholesterol ester

2Cholesterol ester + Saturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Saturated triglyceride

2Cholesterol ester + Unsaturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Unsaturated triglyceride

As figure 4 shows, the muscle compartment also is divided into two sections, muscle tissue and muscle capillary. In muscle capillary, the processes included are VLDL metabolism, chylomicron metabolism and CETP exchange process. In VLDL metabolism, VLDL becomes IDL by giving up triglycerides which are hydrolyzed by lipoprotein lipase, and IDL either becomes LDL by giving up triglycerides which are hydrolyzed by hepatic lipase, or IDL is directly endocytosed by receptors. Chylomicron becomes chylomicron remnant by giving up triglycerides which are hydrolyzed by lipoprotein lipase. CETP transfers cholesterol esters from

HDL to both VLDL/IDL and transfers triglycerides back to HDL from VLDL/IDL. In muscle tissue, the processes included are beta-oxidation and balance reaction among monoglycerides(MGA), diglycerides(DGA) and triglycerides. In beta-oxidation, fatty acids are utilized to produce Acetyl-CoA.

Chapter 3. Results and Discussion

In daily diet, different types of fatty acids are taken is from different sources. In our model, palm oil, olive oil and corn oil (enriched in saturated, monounsaturated and omega-6 polyunsaturated fatty acids respectively) are included and discussed.

	Saturated fatty acids (%)	Monounsaturated fatty acids (%)	Omega-3 fatty acids (%)	Omega-6 fatty acids (%)
Palm oil	49.3	37	0.2	9.1
Olive oil	13.8	73	0.7	9.8
Corn oil	12.9	27.6	1	58

Table 2. Composition of different types of oil

One of the most important parameters need to be determined in our model is the synthesis rate of VLDL and it depends on both ApoB100 production rate and the triglycerides secretion rate in the VLDL assembly process which we found in López-Soldado et al. (2009).[87] With the intake amount of 40 mg for each type of oil, we derived fatty acid distribution in each organ in figure 5. Triglycerides in each organ reach the peak after around 2 hours of dietary intake, and muscle has about 4 times triglyceride as liver. Saturated and unsaturated triglycerides in VLDL for different types of oil are also shown. Corn oil has the highest peak of both saturated and unsaturated triglycerides.

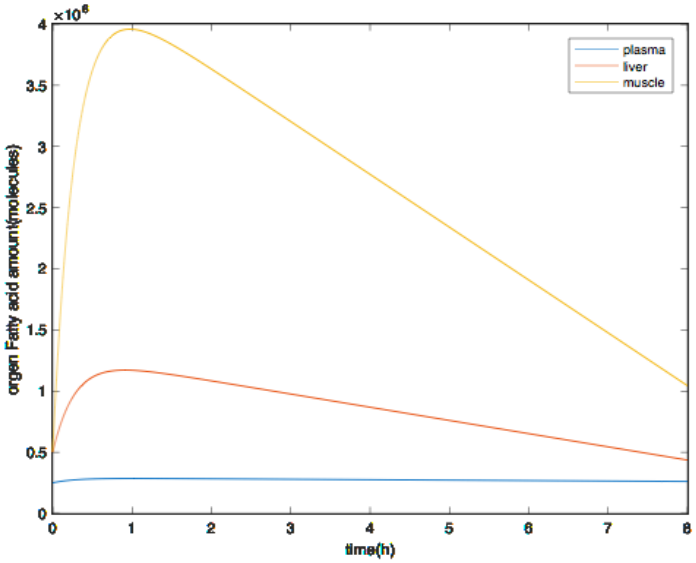


Figure 5. Number of triglycerides in organs

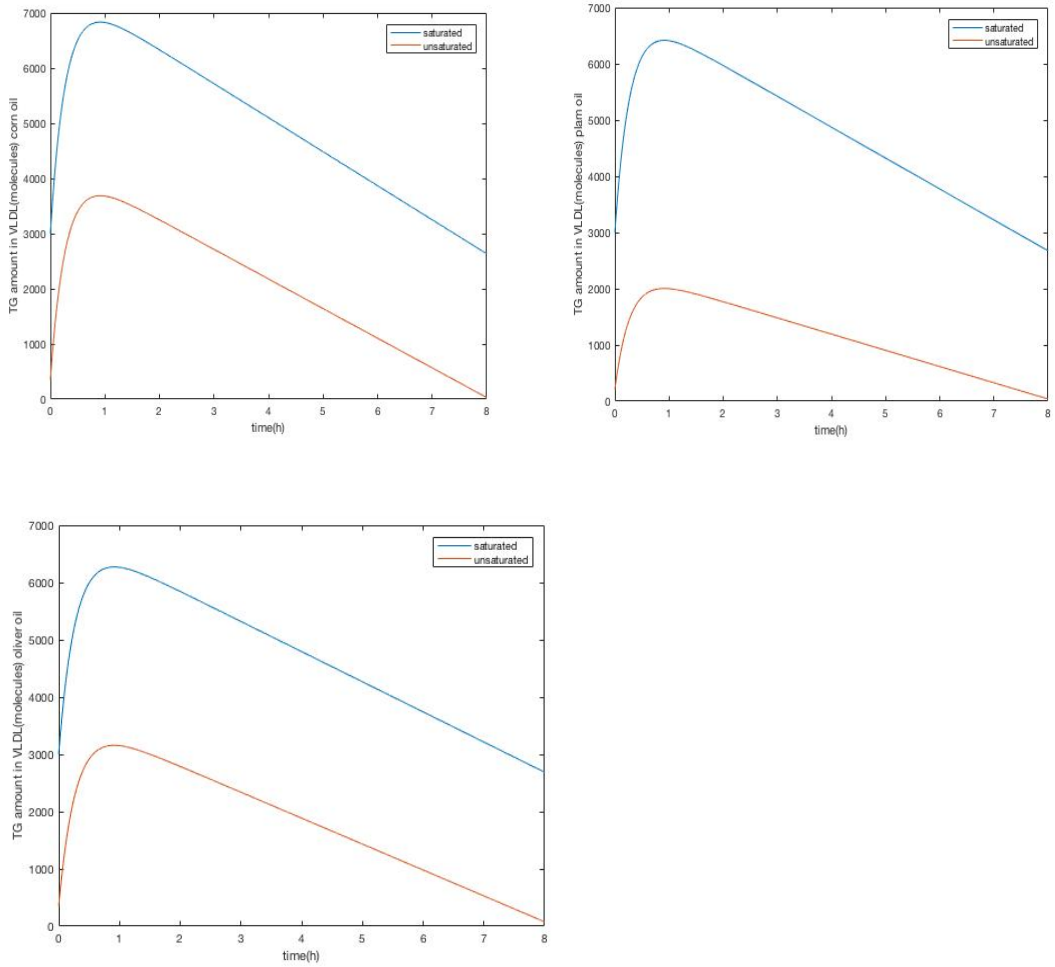


Figure 6. Total and unsaturated triglycerides in oils

Total and unsaturated cholesterol esters for all three types of oil are shown in figure 7. Total cholesterol ester for three oils are the same while unsaturated cholesterol ester for palm oil is less than that of corn oil and olive oil.

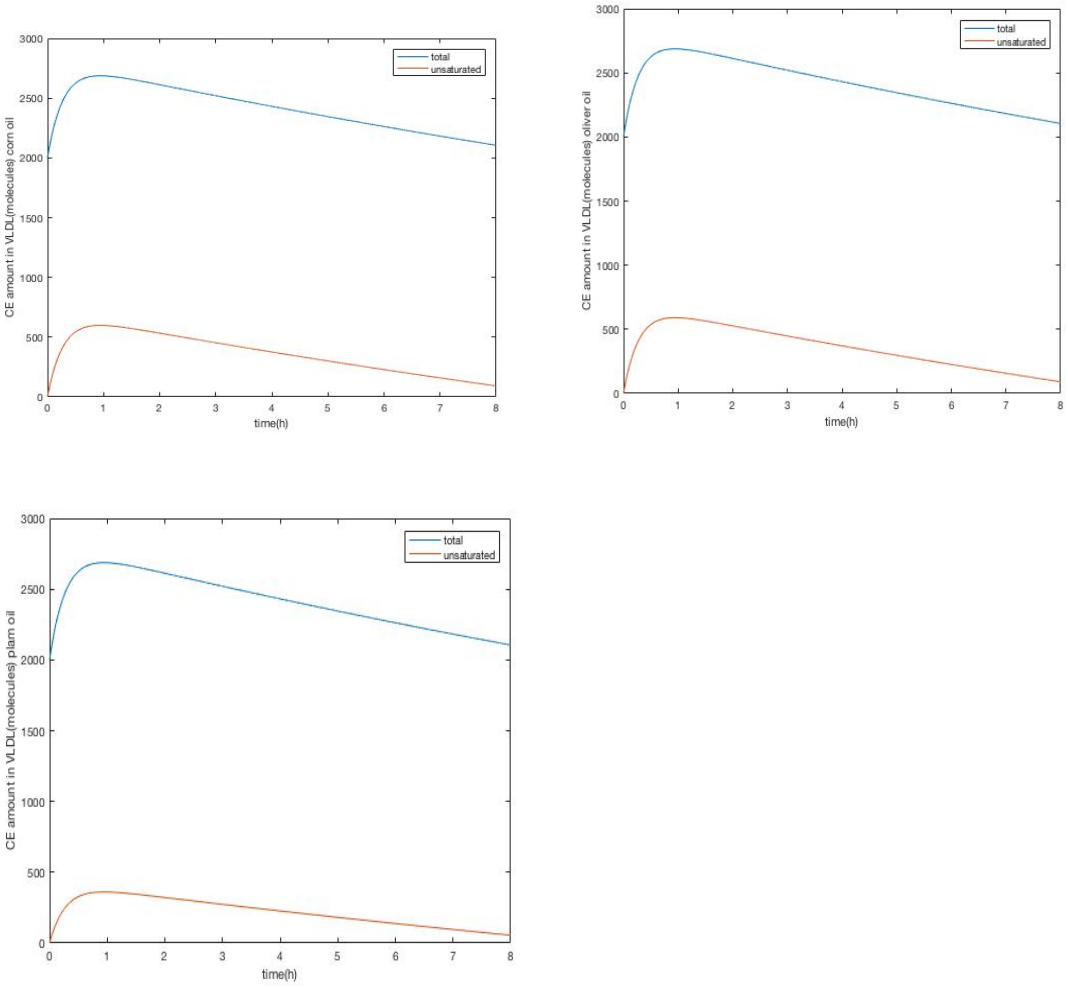


Figure 7. Total and unsaturated cholesterol ester in oils

Double bonds number of three types of oil are shown in figure 8. Corn oil has the maximum numbers of double bonds whereas palm oil has the least numbers of double bonds.

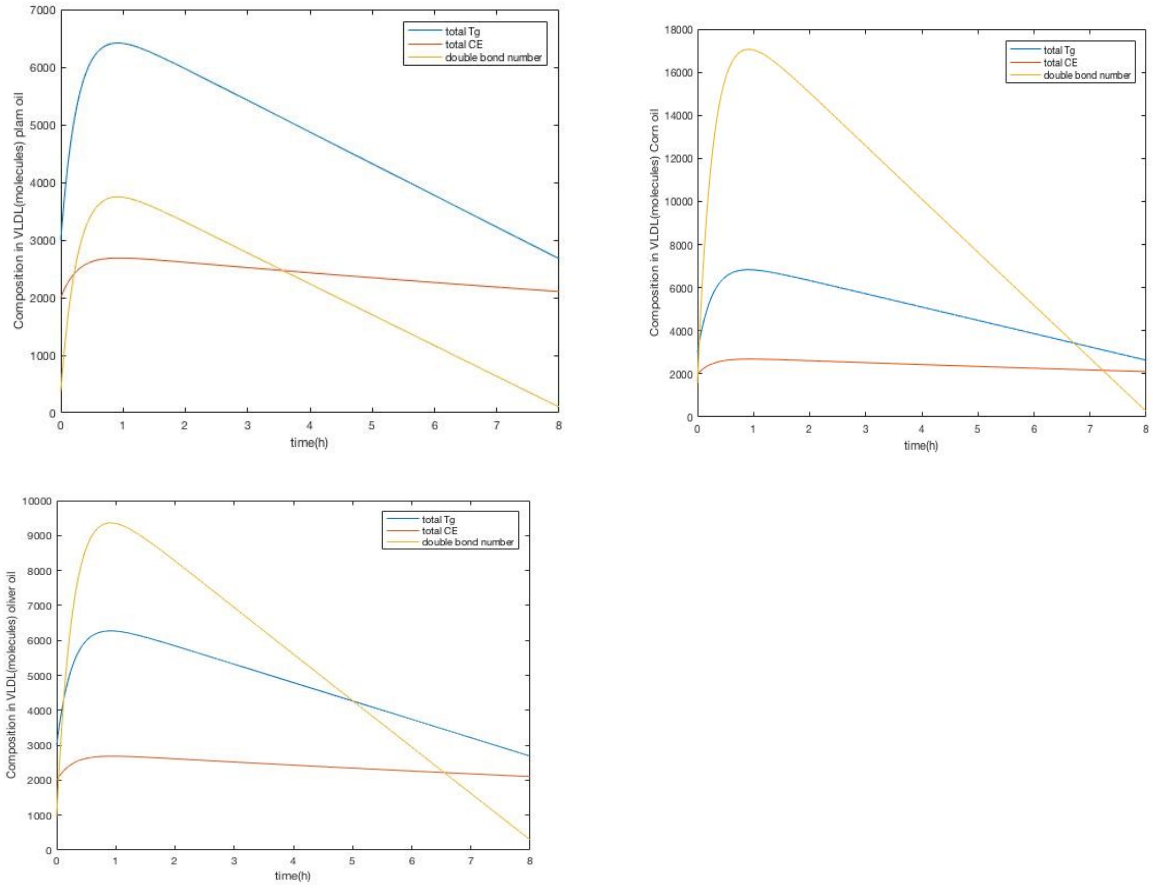
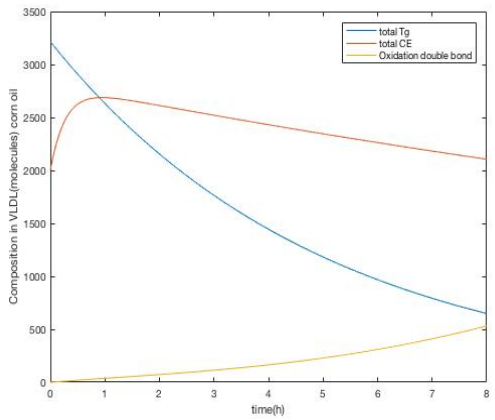
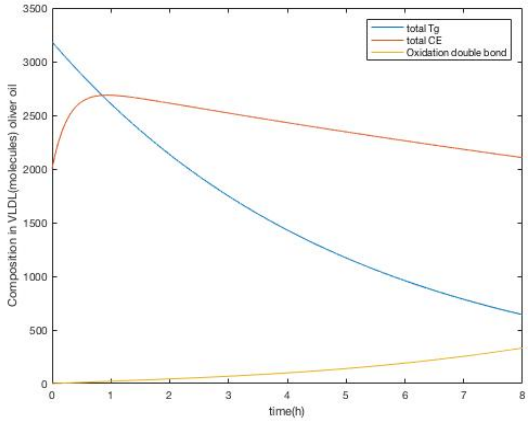


Figure 8. Double bonds number in oils

Figure 9 shows the oxidized double bonds in low triglyceride VLDL and figure 10 shows the oxidized double bonds in high triglyceride VLDL. Both in low triglyceride and high triglyceride VLDL, corn oil has the largest amount of oxidized double bonds while palm oil has the least number of oxidized double bonds.





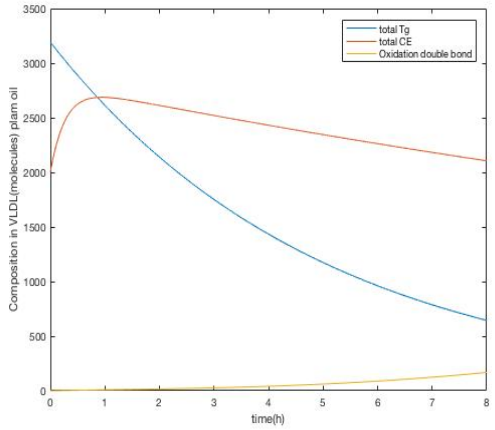
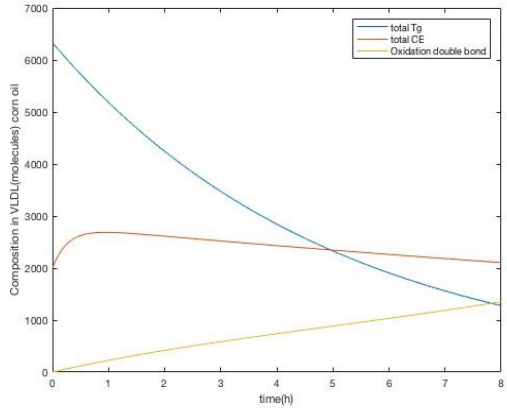
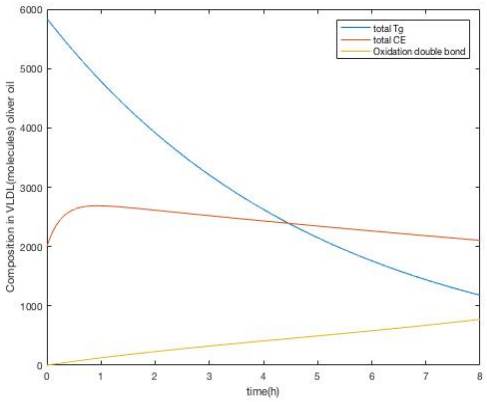


Figure 9. Oxidized double bonds in low triglyceride VLDL





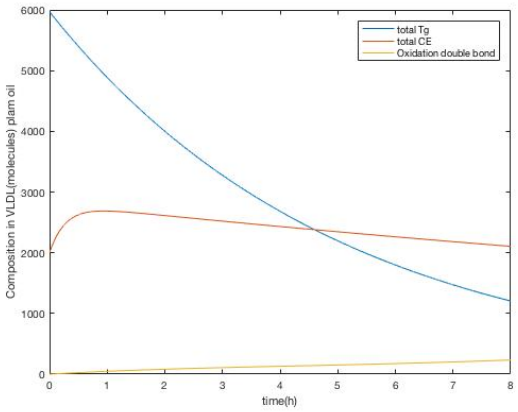


Figure 10. Oxidized double bonds in low triglyceride VLDL

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Appendix

Liver

1. **Unsaturated triglyceride oxidation**

Unsaturated triglyceride + [o] ⟶ oxidized triglyceride

2. **Unsaturated cholesterol ester oxidation**

Unsaturated cholesterol ester + [o] ⟶ oxidized cholesterol ester

3. **Saturated triglyceride hydrolysis**

Saturated triglyceride ⟶ 3 Saturated Fatty acids + Glycerol

4. **Unsaturated triglyceride hydrolysis**

Unsaturated triglyceride ⟶ 3 Unsaturated Fatty acids + Glycerol

5. **Saturated cholesterol ester production**

Cholesterol + Saturated Fatty acid ⟶ Saturated cholesterol ester

6. **Unsaturated cholesterol ester production**

Cholesterol + Unsaturated Fatty acid ⟶ Unsaturated cholesterol ester

7. **MGA/DGA/TG balance**

Fatty acid + Glycerol ⟷ Monoglyceride

Fatty acid + Monoglyceride ⟷ Diglyceride

Fatty acid + Diglyceride ⟷ Triglyceride

8. **VLDL assembly**

Triglyceride + Cholesterol ester + phospholipid + ApoB100 ⟶ VLDL

9. **Beta-oxidation**

Saturated Fatty acid ⟶ nAcetyl-CoA

Unsaturated Fatty acid ⟶ nAcetyl-CoA

10. **Citric acid cycle**

Acetyl-CoA ⟶ ATP

11. **Mevalonate pathway**

3Acetyl-CoA ⟶ Mevalonic acid

12. **CETP transfer processc**

2Saturated triglyceride + Cholesterol ester loading CETP ⟶ Saturated triglyceride loading CETP + 2Cholesterol ester

2Unsaturated triglyceride + Cholesterol ester loading CETP ⟶ Unsaturated triglyceride loading CETP + 2Cholesterol ester

2Cholesterol ester + Saturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Saturated triglyceride

2Cholesterol ester + Unsaturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Unsaturated triglyceride

13. **HDL formation**

ApoA1 + Cholesterol ⟶ HDL

1.

$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{o}] * [\boldsymbol{uTG}]$$

2.

$$-\frac{\mathbf{d[uCHE]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{o}] * [\boldsymbol{uCHE}]$$

3.

$$-\frac{\mathbf{d[sTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{sTG}]$$

4.

$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{uTG}]$$

5.

$$-\frac{\mathbf{d[CH]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CH}] * [\boldsymbol{sFFA}]$$

6.

$$-\frac{\mathbf{d[CH]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CH}] * [\boldsymbol{uFFA}]$$

7.

$$-\frac{\mathbf{d[FFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{FFA}] * [\boldsymbol{GLY}] - \boldsymbol{k'} * [\boldsymbol{MGA}]$$

$$-\frac{\mathbf{d[MGA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{FFA}] * [\boldsymbol{MGA}] - \boldsymbol{k'} * [\boldsymbol{DGA}]$$

$$-\frac{\mathbf{d[DGA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{FFA}] * [\boldsymbol{DGA}] - \boldsymbol{k'} * [\boldsymbol{TG}]$$

8.

$$-\frac{\mathbf{d[CE]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CE}]$$

$$-\frac{\mathbf{d[PL]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{PL}]$$

$$-\frac{\mathbf{d[TG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{TG}]$$

$$-\frac{\mathbf{d[ApoB100]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{ApoB100}]$$

9.

$$-\frac{\mathbf{d[sFFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{sFFA}]$$

$$-\frac{\mathbf{d[uFFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{uFFA}]$$

10.

$$-\frac{\mathbf{d[AcetylCoA]}}{\mathbf{dt}} = \boldsymbol{k} * [\mathbf{AcetylCoA}]$$

11.

$$-\frac{\mathrm{d[AcetylCoA]}}{\mathrm{dt}} = \boldsymbol{k} * [\mathbf{AcetylCoA}]^3$$

12.

$$-\frac{\mathrm{d[sTG]}}{\mathrm{dt}} = \boldsymbol{k} * [\boldsymbol{CCETP}] * [\boldsymbol{sTG}]^2$$

$$-\frac{\mathrm{d[uTG]}}{\mathrm{dt}} = \boldsymbol{k} * [\boldsymbol{CCETP}] * [\boldsymbol{uTG}]^2$$

$$-\frac{\mathrm{d[CE]}}{\mathrm{dt}} = \boldsymbol{k} * [\boldsymbol{sTGCETP}] * [\boldsymbol{CE}]^2$$

$$-\frac{\mathrm{d[CE]}}{\mathrm{dt}} = \boldsymbol{k} * [\boldsymbol{uTGCETP}] * [\boldsymbol{CE}]^2$$

13.

$$-\frac{\mathrm{d[CH]}}{\mathrm{dt}} = \boldsymbol{k} * [\boldsymbol{CH}]$$

Adipose Tissue

1. **Unsaturated triglyceride oxidation**

Unsaturated triglyceride + [o] ⟶ oxidized triglyceride

2. **Unsaturated cholesterol ester oxidation**

Unsaturated cholesterol ester + [o] ⟶ oxidized cholesterol ester

3. **Saturated triglyceride hydrolysis**

(LPL)

Saturated triglyceride ⟶ 3 Saturated Fatty acids + Glycerol

4. **Unsaturated triglyceride hydrolysis**

Unsaturated triglyceride ⟶ 3 Unsaturated Fatty acids + Glycerol

5. **Saturated cholesterol ester production**

Cholesterol + Saturated Fatty acid ⟶ Saturated cholesterol ester

6. **Unsaturated cholesterol ester production**

Cholesterol + Unsaturated Fatty acid ⟶ Unsaturated cholesterol ester

7. **MGA/DGA/TG balance**

Fatty acid + Glycerol ⟷ Monoglyceride

Fatty acid + Monoglyceride ⟷ Diglyceride

Fatty acid + Diglyceride ⟷ Triglyceride

8. **Beta-oxidation**

Saturated Fatty acid ⟶ nAcetyl-CoA

Unsaturated Fatty acid ⟶ nAcetyl-CoA

9. **Citric acid cycle**

Acetyl-CoA ⟶ ATP

10. **CETP transfer process**

2Saturated triglyceride + Cholesterol ester loading CETP ⟶ Saturated triglyceride loading CETP + 2Cholesterol ester

2Unsaturated triglyceride + Cholesterol ester loading CETP ⟶ Unsaturated triglyceride loading CETP + 2Cholesterol ester

2Cholesterol ester + Saturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Saturated triglyceride

2Cholesterol ester + Unsaturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Unsaturated triglyceride

11. HDL formation

ApoA1 + Cholesterol ⟶ HDL

1.

$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{o}] * [\boldsymbol{uTG}]$$

2.

$$-\frac{\mathbf{d[uCHE]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{o}] * [\boldsymbol{uCHE}]$$

3.

$$-\frac{\mathbf{d[sTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{sTG}]$$

4.

$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{uTG}]$$

5.

$$-\frac{\mathbf{d[CH]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CH}] * [\boldsymbol{sFFA}]$$

6.

$$-\frac{\mathbf{d[CH]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CH}] * [\boldsymbol{uFFA}]$$

7.

$$-\frac{\mathbf{d[FFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{FFA}] * [\boldsymbol{GLY}] - \boldsymbol{k'} * [\boldsymbol{MGA}]$$

$$-\frac{\mathbf{d[MGA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{FFA}] * [\boldsymbol{MGA}] - \boldsymbol{k'} * [\boldsymbol{DGA}]$$

$$-\frac{\mathbf{d[DGA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{FFA}] * [\boldsymbol{DGA}] - \boldsymbol{k'} * [\boldsymbol{TG}]$$

8.

$$-\frac{\mathbf{d[sFFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{sFFA}]$$

$$-\frac{\mathbf{d[uFFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{uFFA}]$$

9.

$$-\frac{\mathbf{d[AcetylCoA]}}{\mathbf{dt}} = \boldsymbol{k} * [\mathbf{AcetylCoA}]$$

10.

$$-\frac{\mathbf{d[sTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CCETP}] * [\boldsymbol{sTG}]^2$$

$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CCETP}] * [\boldsymbol{uTG}]^2$$

$$-\frac{d[CE]}{dt} = k * [sTGCETP] * [CE]^2$$

$$-\frac{d[CE]}{dt} = k * [uTGCETP] * [CE]^2$$

11. $$-\frac{d[CH]}{dt} = k * [CH]$$

Muscle

1. **Unsaturated triglyceride oxidation**

Unsaturated triglyceride + [o] ⟶ oxidized triglyceride

2. **Unsaturated cholesterol ester oxidation**

Unsaturated cholesterol ester + [o] ⟶ oxidized cholesterol ester

3. **Saturated triglyceride hydrolysis**

Saturated triglyceride ⟶ 3 Saturated Fatty acids + Glycerol

4. **Unsaturated triglyceride hydrolysis**

Unsaturated triglyceride ⟶ 3 Unsaturated Fatty acids + Glycerol

5. **Saturated cholesterol ester production**

Cholesterol + Saturated Fatty acid ⟶ Saturated cholesterol ester

6. **Unsaturated cholesterol ester production**

Cholesterol + Unsaturated Fatty acid ⟶ Unsaturated cholesterol ester

7. **Beta-oxidation**

Saturated Fatty acid ⟶ nAcetyl-CoA

Unsaturated Fatty acid ⟶ nAcetyl-CoA

8. **Citric acid cycle**

Acetyl-CoA ⟶ ATP

9. **CETP transfer process**

2Saturated triglyceride + Cholesterol ester loading CETP ⟶ Saturated triglyceride loading CETP + 2Cholesterol ester

2Unsaturated triglyceride + Cholesterol ester loading CETP ⟶ Unsaturated triglyceride loading CETP + 2Cholesterol ester

2Cholesterol ester + Saturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Saturated triglyceride

2Cholesterol ester + Unsaturated triglyceride loading CETP ⟶ Cholesterol ester loading CETP + 2Unsaturated triglyceride

10. **HDL formation**

ApoA1 + Cholesterol ⟶ HDL

1.
$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{o}] * [\boldsymbol{uTG}]$$

2.
$$-\frac{\mathbf{d[uCHE]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{o}] * [\boldsymbol{uCHE}]$$

3.
$$-\frac{\mathbf{d[sTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{sTG}]$$

4.
$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{uTG}]$$

5.
$$-\frac{\mathbf{d[CH]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CH}] * [\boldsymbol{sFFA}]$$

6.
$$-\frac{\mathbf{d[CH]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CH}] * [\boldsymbol{uFFA}]$$

7.
$$-\frac{\mathbf{d[sFFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{sFFA}]$$
$$-\frac{\mathbf{d[uFFA]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{uFFA}]$$

8.
$$-\frac{\mathbf{d[AcetylCoA]}}{\mathbf{dt}} = \boldsymbol{k} * [\mathbf{AcetylCoA}]$$

9.
$$-\frac{\mathbf{d[sTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CCETP}] * [\boldsymbol{sTG}]^2$$
$$-\frac{\mathbf{d[uTG]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CCETP}] * [\boldsymbol{uTG}]^2$$
$$-\frac{\mathbf{d[CE]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{sTGCETP}] * [\boldsymbol{CE}]^2$$
$$-\frac{\mathbf{d[CE]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{uTGCETP}] * [\boldsymbol{CE}]^2$$

10.
$$-\frac{\mathbf{d[CH]}}{\mathbf{dt}} = \boldsymbol{k} * [\boldsymbol{CH}]$$

Curriculum Vitae

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Summary Statement

Chemical Engineering student with abundant research experience relevant to biochemistry field. Effective problem-resolver in biochemical aspect especially in metabolic biotechnology and pharmacology.

Education

University of Massachusetts, Amherst
Amherst, MA Bachelor of Science, Chemical Engineering (GPA 3.42)
January 2014 - May 2017 Concentration: Biochemical Engineering
Relevant Course: Probability, Statics, Calculus, Algebra, Math Modeling, Physical Chemistry, Kinetics and Reactor Designs, Thermodynamics, Fluid Mechanics, Heat and Mass Transfer, Separations, Organic Chemistry, Biochemistry for Chemists, Bioengineering, Process control, Process design, Tissue Engineering, Nanobiomaterials

Johns Hopkins University
Baltimore, MD Master of Science in Engineering, Chemical and Biomolecular Engineering
September 2017 - May 2019
Honor: ChemBE Master Second Year Scholarship (2018-2019)
Relevant Course: Advanced Thermodynamics, Metabolic system Biotechnology, Interfacial Science, Advanced Chemical Reaction, Transport Phenomena, Advanced Pharmacokinetics, Advanced Pharmacodynamics

Project Experience

University of Massachusetts, Amherst, **Department of Chemical Engineering**
Amherst, MA Bone Marrow Engineering Project
September 2015 - May 2016

- Created and developed multi-compartment tissue model via integrating separately constructed and optimized individual modules in a single platform
- Supervised the model creation process, collected data and tested stability of the model

University of Massachusetts, Amherst, **Drug Delivery Lab**
Amherst, MA Research Assistant
September 2015 - May 2016

- Created the *in vitro* devices that mimic the tissue surrounding blood vessels in tumors and enable measurement of diffusion, cell binding, and therapeutic outcome by understanding the integration of computational models, microfluidic devices, and animal models
- Organized lab instruments and utilized the software to collect lab data

Johns Hopkins University
Baltimore, MD Advanced Pharmacokinetics Project
September 2017 – May 2018

- In a three people team developed a model by MATLAB under multi-compartment environment to predict hepatic bioavailability with given pharmacokinetics parameters of drugs

Leadership and Activities

Heat Exchange Research Group in Senior Lab
Amherst, MA Team leader
September 2016-November 2016

- Distributed specific work to group members and integrated final results from research
- Made presentations and wrote final lab report

UMass Marching Band
Amherst, MA Trombone player
January 2014-May 2015

- Attended the school sports marching openings and other activities that needed marching band performance

IPO (International Program Office)
Amherst, MA Volunteer
September 2016

- Participated in helping new students during International Orientation at the beginning of the semester

Technical Skills

Software: Microsoft Office Suit (Word, Excel, PowerPoint), MATLAB, Aspen, Simulink
Foreign Language: Chinese, Japanese